FEE

DP Barcode: 349941, 365449; **Reg. No./File Symbol No.**: 7969-ETL; **Product Name**: BAS 800H Herbicide technical (Saflufenacil)

Chemistry data review for the registration of a technical grade of active ingredient (TGAI) "BAS 800H Herbicide technical (Saflufenacil)".

Product Chemistry Data Requirements

Date: 09/21/09
EPA File Symbol No.: 7969-ETL
Product Name: BAS 800 H
Active Ingredient: Saflufenacil
Submission Number / DP Barcode: D349941;
Decision No.: 389161

PMRA Submission No. : 2008-0431
CANADA Product Name : Kixor

APVMA File Number : 62869
Application Number : 44138

Source Code / PC Code: 118203
Uses: Food use

FROM: Shyam Mathur, Product chemistry Team Leader, Technical Review Branch/RD (7505 P)

TO: Kathryn Montague / Joanne Miller, RM 23; Herbicide Branch / RD (7505P)

Manufacturing Plant Location:

Primary Manufacturing Site:
Contact Person: Jan Wevers, Technology Leader, BASF Aktiengesellschaft, Carl-Bosch-Strasse 38; 67056 Ludwigshafen Germany; Tel. No.: + 49 021 60-78497; Fax No.: + 49 021 60-56415; e-mail: jan.wevers@basf.com

EPA Applicant's / Registrant's Name and Address: BASF Corporation, Agricultural Products Division, 26 Davis Drive, P. O. Box 13528, Research Triangle Park North Carolina 27709, USA.
Contact Person: Craig D. Kleppe, Product Registration manager; Telephone: +1 919 547 2615; Telefax: + 1 919 547 2850; E-mail: craig.kleppe@basf.com

PMRA Applicant's Name and Address: BASF Canada Inc., 5th floor, 100 Milverton Drive, Mississauga, ON, Canada, L5R 4H1. Contact person: Raj Sandhu, Telephone 1-289-360-6030, raj.sandhu@basf.com

APVMA Applicant's Name and Address: BASF Australia Ltd., 500 Princes Highway, Noble Park, Victoria 3174 Australia. Contact person: Gavin Heard, +61 3 9212 1614, Telefax: +61 3 9212 1511, gavin.heard@basf.com .

Guarantee: 97.4% nominal (limits: 94.5-100%)

INTRODUCTION:

Reference: T. Hsieh: "BASF Proposal to commercially produce the Anhydrate form of BAS 800 H Technical'; BASF DocID 2007/7013587; MRID No. 471278-05

BAS 800 H is a new herbicide active ingredient currently in development by BASF Corporation. BAS 800 H is targeted for use as a herbicide in field & row crops, groves, orchards, vineyards, pine plantations and in non-crop applications in North America and Australia.

During the discovery and developmental phases, two predominant crystalline physical forms of BAS 800 H technical material have emerged and been subsequently synthesized and evaluated. The physical forms, known as the hydrate (or monohydrate) form and the anhydrate form, are both viable future options for manufacture during commercial-scale production of BAS 800 H. The hydrate form has been the focal point during most of the development phase for BAS 800 H, and in particular the form used in developing the core data set, including toxicological studies. However, as realized during manufacturing scale-up trials, the anhydrate form offers some distinct advantages from a production standpoint. Therefore, BASF proposes to synthesize the anhydrate form during commercial-scale production of BAS 800 H technical grade material.

It is common to have different physical forms of a chemical that occurs in a crystalline solid state. The 2 most important physical forms of technical grade BAS 800 H are the **crystalline anhydrate** and **crystalline hydrate (monohydrate)**. Both forms are crystalline solids with the same chemical structure, molecular weight and CAS number (CAS RN 372137-35-4). Their composition is also the same, although the hydrate form contains one molecule of water for each molecule of BAS 800 H active ingredient within the crystalline lattice structure, whereas the anhydrate form is without water within the crystalline lattice structure. It can be said that the anhydrate form is a more pure form of the chemical because of the absence of water. There is no difference in the chemical route of synthesis for both crystalline forms, but the production of the hydrate form requires the addition of water before crystallization (the final step in synthesis), whereas the anhydrate does not require the addition of water.

Note: the three reviewing countries agreed that the identification of the anhydrous and monohydrate forms of saflufenacil as identical is not valid, and that they are two different chemicals.

Note: In the BASF response (dated May 12, 2009), this issue was explained. All the three reviewing countries now agree that the anhydrous & monohydrate forms are same and are not considered different molecules (confirmed on telephonic conversation with Katherine-Kepple Jones (PMRA) on 09-23-09.

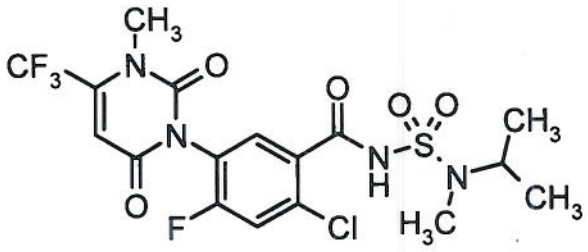
During the initial stages of BAS 800 H process development, the hydrate form was first synthesized in the laboratory (i.e., bench scale production) and certified as two

different material batches (COD-000227 and COD-000298). Similarly, during the first phase of scale-up operations, BAS 800 H hydrate was produced in a pilot plant and certified as two different material batches (COD-000515, COD-000606). As such, the hydrate form was used in all toxicology studies conducted for product registration purposes, including acute, genotox, teratology, reproduction, and sub-chronic and chronic feeding studies (rat, mouse, dog).

However, during the course of synthesis process optimization and further pilot plant trials, drying experiments showed that it was difficult to obtain the pure hydrate form on a commercial scale, since the hydrate form loses water easily under normal drying conditions, especially using the existing and standard drying equipment. For the consideration of future production scale-up, the data from the drying experiments indicate that drying of the pure crystalline hydrate is expected to be very difficult if not impossible to control and manage. If not controlled properly, each batch of technical material would probably have different percentages of the different crystalline forms. For proper quality control during commercial scale production to maintain a pure crystalline hydrate form, specific drying conditions will be required, which in turn will necessitate an expensive investment into specialized drying equipment. On the other hand, the production of the anhydrate does not require the addition of water prior to crystallization, the crystallization can be conducted in smaller vessels and drying can then be done in standard and existing drying equipment. Drying for the anhydrate form will be more consistent and reproducible, because the only the process solvent(s) need to be removed completely, whereas the water content is not an issue.

Therefore, BASF prefers to focus on optimizing commercial scale production of the anhydrate, rather than resolving technical and operational difficulties with production of the hydrate. Ultimately, it will be more economical to produce the anhydrate form of BAS 800 H technical material, both from an investment as well as an operational standpoint, and the inter-batch variability in technical grade material will be reduced.

The guideline study to generate 5-batch analytical data to determine the composition of BAS 800 H technical, that being Preliminary analysis OPPTS 830.1700 (see report **BASF RegDoc DocID 2007/1022325**) was conducted on a combination of hydrate and anhydrate technical material. The 5-batch analysis consisted of technical material from four batches of hydrate (batch# COD-000227, COD-000298, COD-000515 and COD-000606) and one batch of anhydrate (batch # 31896/082). As mentioned above, the only difference between hydrate and anhydrate technical material is the amount of water in the sample. Therefore, based on the intended commercial production of the anhydrate form of BAS 800 H technical material, the product composition and specification that is reflected in the Confidential Statement of Formula submitted under Certified Limits, OPPTS 830.1750 for BAS 800 H herbicide technical is based only on the anhydrate form of BAS 800 H technical material.

Table 1. Product Identity of: BAS 800H		
DACO # / GLN / OECD	Title	Data/Information
2.3 / 830.1000 / IIA 1.5.2	Trade Name	BAS 800 H (in USA) Kixor (in Canada)
2.3.1 / 830.1000 / IIA 1.5.1	Other Name	"Kixor"
2.4 / 830.1550 / IIA 1.3	Common Name	SAFLUFENACIL
2.5 / 830.1550 / IIA 1.4	ISO Chemical Name	*N'*-{2-chloro-4-fluoro-5-[1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]benzoyl}-*N*-isopropyl-*N*-methylsulfamide
	CAS Chemical Name	2-chloro-5-[3, 6-dihydro-3-methyl-2, 6-dioxo-4-(trifluoromethyl)-1(2H)-pyridimidinyl]-4-fluoro-N[[methyl (1-methyl ethyl)amino]sulfonyl]benzamide
2.6 / 830.1550 / IIA 1.6	CAS Number	372137-35-4
2.7 / 830.1550 / IIA 1.7	Structural Formula	
2.8 / 830.1550 / IIA 1.7	Molecular Formula	$C_{17}H_{17}ClF_4N_4O_5S$
2.9 / 830.1550 / IIA 1.7	Molecular Weight	500.86

SUMMARY OF FINDINGS:

1. The registrant has submitted a Confidential Statement of Formula for basic formulation (12-19-07) for the BAS 800H (saflufenacil) TGAI/MUP produced at pilot plant scale. The average purity of the AI in TGAI/MUP is 97.4% (anhydrate), as determined by the five batch analysis. The proposed certified limits for the AI are based on the standard certified limits as set forth in 40CFR§158.175(b) (2), the certified limits for the impurities are based on the five batch analysis. The product chemistry data submitted corresponding to guideline reference 830.1550 (product identity & composition) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.155 and 158.175 respectively [MRID No. 471278-05 and 472278-06].

2. The product chemistry data submitted corresponding to guideline reference 830.1600 (description of material used to produce the product) satisfy the data requirements of 40CFR§ 158.160 [MRID No. 471278-02].

3. The product chemistry data submitted corresponding to guideline reference 830.1620 (description of production process) not satisfy the data requirements for 40CFR§158.162. The proposed BAS800H TGAI / MUP was manufactured on pilot plant scale [redacted] The details of the production process have been provided which included the amounts of each starting material used in the process, description of the equipment used, the reaction conditions (temperature, pH, etc.) and the yields of the final product and the steps taken to control the quality of the product.

4. The product chemistry data submitted corresponding to guideline reference 830.1670 (discussion on the formation of impurities) satisfy the data requirements for 40CFR§158.167. During the production of the BAS 800 H TGAI/MUP, the registrant discussed and reported the formation of [redacted] The discussion has been provided on theoretical possible impurities and the impurities which are present at levels of < 0.1%. There is one impurity of toxicological concern present in the TGAI/MUP. TRB has no knowledge on the toxicity of the other impurities present in the TGAI/MUP [MRID No. 471278-02].

5. The data submitted corresponding the guideline reference 830.1700 (preliminary analysis) satisfy the data requirements of 40CFR§158.170. The five batch analysis was conducted under GLP in compliance with 40CFR§160. Five representative batches (four batches as monohydrate & one as anhydrate) of the BAS 800 H TGAI/MUP produced in Germany were analyzed for percent active ingredient and the impurities by BASF analytical laboratory in Germany. The active ingredient & the impurity contents were determined by HPLC-UV (271nm) with external standard method. The five batch analysis supported the proposed basic CSF (dated 12-19-07). The monohydrate toxbatches examined contain between 93.5% and 94.6% pure AI. The anhydrous tox batch contains 99.1% pure AI. The identity of the active ingredient was confirmed by coincidence of the HPLC retention time with authentic reference item according to the method APL0498/01 and by IR spectroscopy. [redacted]

6. The data submitted corresponding the guideline reference 830.1800 (enforcement analytical method) satisfy the data requirements of 40CFR§158.180. The purity of the AI in the TGAI was determined by HPLC-UV external standard method. The HPLC-UV method employed a Eclipse XDB-C18, 4.6 x 150 mm, 3.5 µm column with UV detector operating at 271 nm. The method validation covered aspects viz., specificity, linearity, precision (% RSD), and accuracy (% recovery) [MRID No. see Table 3].

7. The data submitted corresponding to guidelines 830 Series Subgroup B (physical-chemical properties) satisfy the data requirements of 40CFR§158.190, except for one year storage stability (830.6317), and corrosion characteristics (830.6320) studies. The registrant has submitted the results of these studies which have not been conducted under GLP requirements [MRID No. See Table 2]

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for BAS 800H TGAI / MUP and has concluded that:

1. All the product chemistry data submitted for BAS 800H (produced on small scale) corresponding to 830 Series Subgroup A are acceptable.

2. The CSF for basic formulation (dated 12-19-07) is acceptable and is supported by five batch analysis.

3. The data submitted corresponding to the 830 Series Subgroup B (physical-chemical properties) are acceptable except for 830.6317 (one year storage stability), and 830.6320 (corrosion characteristics).

4. The registrant must generate studies corresponding to guidelines 830.6317(one year storage stability) and 830.6320 (corrosion characteristics). The observations must be made at 0, 3, 6, 9, & 12 month intervals. These studies must be conducted under the full GLP requirements in compliance with 40CFR§160.
[**Note**: Not required by PMRA for TGAI; APVMA requires accelerated study as well as 12 month study]

5. The Agency will require that the registrant resubmit the 830 series group A data (including a revised basic CSF) for the BAS 800H TGAI/MUP when the product is produced on commercial scale.

[**Note**: PMRA & APVMA require only if manufacturing process is changed or new impurities are detected]

6. PMRA and/or APVMA would also like to see the following:

a) GLP five-batch data for [redacted] to be undertaken once commercial production begins, and a corresponding GLP method validation study (under a future application)

Good Laboratory Practices Compliance Statement:

The studies contained within this report were conducted in accordance with the Good Laboratory Practice Standards as specified in 40 CFR 160, by OECD or by the German Chemikaliengesetz, the latter two of which have recognized differences from the standards of FIFRA and TSCA.

yes [X] no [ ] not stated / applicable [ ]

The exceptions which were stated not to be GLP-compliant include storage stability, confirmation of identity, and validation of the analytical method for [redacted] PMRA does not require storage stability for a TGAI, and will not ask for the confirmation of identity to be GLP, but will require GLP data for the [redacted] method validation once commercial-scale production begins.

Chemical and Physical Properties: See Table 2.

Reference: See the Author name, MRID Nos. & Report Nos. in column 4 of Table 2.

Table 2. Chemical & physical properties.

DACO # / GLN	Title	Test substance purity (%)	MRID / Report #	Status[1]	Result[2] or Deficiency
2.14.1 / 830.6302	Colour	TGAI/MUP 97.4%	R Yacoub 47127812 #132485	A	White
2.14.2 / 830.6303	Physical state	" "	" "	A	Solid powdery
2.14.3 / 830.6304	Odor	" "	" "	A	Odorless
2.14.4 / 830.7200	Melting point/range	PAI, 99.6%	R. Yacoub 47127816 2005/ 5000147	A	189.9°C (DSC) with a peak maximum of 193.4°C. BAS 800 H (PAI) is also stable under nitrogen up to 220°C.
2.14.5 / 830.7220	Boiling point/range			NA	
2.14.6 / 830.7300	Density at 20°C	PAI 99.6%	T.Kroehl 47127821 #132464-1	A	1.595 g/cc at 20°C
	Bulk density at room temperature	TGAI/MUP 97.4%	R Yacoub 47127812 #132485	A	Free fall = 0.661 kg/l Packed = 0.736 kg/l

Table 2. Chemical & physical properties.

DACO # / GLN	Title	Test substance purity (%)	MRID / Report #	Status[1]	Result[2] or Deficiency
2.14.7 / 830.7840	Water solubility at 20°C	PAI 99.6%	C.Vanhook 47127819 2005/ 7003391	A	Shake flask method. Analytical method: HPLC-UV (271 nm) Column: YMC J'Sphere ODS C18 (20 cm x 4.6 mm x 4 µm) pH — solubility (g/100 ml) 4 (buffer) — 0.0014 5 (buffer) — 0.0025 7 (buffer) — 0.21 9 (buffer) — could not be determined due to degradation
2.14.8 / 830.7860	Solvent solubility at 20°C	TGAI/MUP 95.4%	C. Vanhook 47127820 2007/ 7001658	A	Solvent — Solubility (g/100 ml) Acetonitrile — 19.4 Dichloromethane — 24.4 N,N-Dimethylformamide — 55.4 Acetone — 27.5 Ethyl acetate — 6.55 Tetrahydrofuran — 36.2 Butyrolactone — 35.0 Methanol — 2.98 Isopropyl alcohol — 0.25 Toluene — 0.23 Olive oil — 0.01 1-Octanol — < 0.01 n-Heptane — < 0.005
2.14.9 / 830.7950	Vapour pressure at 20°C	PAI 99.6%	T.Kroehl 47127821 #132464-1 2005/10264 64	A	$< 10^{-10}$ Pa, showing the substance to be non-volatile 4.5×10^{-15} Pa @ 20°C 2.0×10^{-14} Pa @ 25°C
830.7000	pH at 25°C	TGAI 97.4%	R Yacoub 47127812 #132485	A	4.426 (1% suspension)
2.14.10 / 830.7370	Dissociation constant (pK_a)	PAI 99.9%	J. Beery 47127817 2007/ 7002007	A	pKa = 4.41 ± 0.025 UV absorption method was used.
2.14.11 / 830.7550 830.75608 30.7570	Octanol/water partition coefficient (P_{ow})	TGAI/MUP 95.4%	C. Vanhook 47127818 2005/ 7004256	A	Po/w — log Pow 368.3 — 2.6 HPLC-UV (230 nm) method was used
2.14.12 / 830.7050	UV/visible absorption spectrum (indicate conditions, if any)	PAI 99.9%	J.Beery 47127815 2005/ 7004339	A	pH — λ max (nm) — ε (l/mol –cm) 1.12 (acidic) — 271.8 — 9539 6.94 (neutral) — 271.4 — 9708 11.69 (basic) — 309.4 — 2358

Table 2. Chemical & physical properties.					
DACO # / GLN	Title	Test substance purity (%)	MRID / Report #	Status[1]	Result[2] or Deficiency
2.14.13 / 830.6313	Stability (temperature, metals, sunlight)	Not provided	R. Yacoub 47127813 2007/ 7007671	A	Test substance was stable at room temperature and 54°C for two weeks when put in contact with Fe, Al and the corresponding acetate salts. The test substance was also stable at RT & 54°C for two weeks.
2.14.14 / 830.6317	Storage stability	TGAI/MUP, purity not provided	G. Genari 47127814	U	This study was not conducted under GLP. Test substance was stable for 2 yrs in HDPE containers at RT and no corrosion was observed in the containers inside and outside.
	Henry's Law Constant	TGAI/MUP	R. Paulick 47127822 2007/ 70113512	A	Hi = 4.01 x 10^{-20} atm –m 3/mol Very low volatilization potential at 25°C
[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable; U = Upgrade [2] Refer to CBI Appendix A for details.					

Data Submitted: See Table 3.

Table 3. Identity and Composition Data for the BAS 800H TGAI/MUP				
DACO # / GLN	Title	MRID / Report #	Status[1]	Details and/or Deficiency[2]
2.12.2 / 830.1550	Product Identity and Disclosure of Ingredients	T. Hsieh 47127805 2007/7013587 S. Brunt; G.Genari 47127806 2007/7013642	A	BAS800 H exists in two predominant crystalline physical forms known as hydrate (monohydrate) form and anhydrate form. Both forms are crystalline solids with same chemical structure, molecular weight and CAS number. The NC of AI (97.4% on dry basis) is supported by 5 batch analysis & agrees with the label claim NC (97.4%). [redacted]
2.11.2, 2.11.3 / 830.1600 830.1620	Starting Materials & Manufacturing Process	G. Genari 47127802 2007/1022324	A	The description and composition for all the starting materials used for the production of BAS 800H tgai/mup have been provided. The TGAI/MUP was produced in small scale, using [redacted] The production process has been described in full detail. The reaction conditions, amounts of chemicals in each step, duration of time, and the yields in each step have been provided. The QA steps involved in each step have been described.
2.11.4 / 830.1670	Discussion of Impurities	" " "	A	The registrant has provided the complete mechanisms of formation, quantification and identification of all the impurities present at levels ≥ 0.1%. [redacted] There is one inorganic impurity of tox concern reported in the CSF. The registrant has provided discussion on the formation of theoretically possible impurities.

Table 3. Identity and Composition Data for the BAS 800H TGAI/MUP

DACO # / GLN	Title	MRID / Report #	Status[1]	Details and/or Deficiency[2]
2.13.3 / 830.1700	Preliminary Analysis	G. Genari 47127803 2007/1022325 47127810 2006/1027568 R. Dotzer 47127804 2007/ 1057829 V.Reiger 47127809 2006/1027567 R. Doetzer 47749002 2007/1057532	A	Five representative batches (produced in pilot plant scale) of the BAS 800H tgai/mup were analyzed for percent active ingredient and the impurities. The 5 batch analysis was conducted on combination of batches consisting of 4 batches of hydrate tgai/mup and one batch of anhydrate tgai/mup. The purity of the AI in the TGAI was determined by HPLC-UV (271 nm) using external calibration with authentic reference item. The [redacted] The structures of the active ingredient and the impurities were confirmed by ESI MS/MS spectra in LC-MS analyses and by proton NMR spectra of isolated fractions in LC-NMR mode. All structures were later confirmed by synthesis of reference standards, which have identical spectra (applicant is to provide these). The five batch analysis supported the CSF for basic formulation. Additional data provided on the NMR & MS of the test substance, the impurities and the corresponding reference substances.
2.12.1 / 830.1750	Certification of Limits	S. Brunt; G. Genari 47127806 2007/7013642	A	The proposed certified limits for the AI are based on the standard certified limits and the proposed certified limits for the impurities are based on five batch analysis results.
2.13.1 / 830.1800	Enforcement Analytical Methods	J.Distler G.Genari 47127807 2005/1018447 47127808 2005/1018448	A	Method AOL0498/01 was to determine the AI content in tgai/mup using RPHPLC-UV with external standard calibration. The AI was quantitated by comparing the peak areas of authentic reference BAS800H of known purity. The method validation was conducted by determination of linearity, precision, accuracy and specificity. [redacted]

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] Refer to CBI Appendix A for details.

ATTACHMENT: CONFIDENTIAL APENDIX

Pages 10-38 Manufacturing process information may be entitled to confidential treatment